

Dkt. #784-A-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : LIN, et al.

U.S. Serial No.: 10/648,081

Filed : August 25, 2003

For : MODEL EPITHELIAL CELL CULTURES

Law Offices of Albert Wai-Kit Chan, LLC  
World Plaza, Suite 604  
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Whitestone, NY 11357

December 02, 2003

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**COMMUNICATION TO SUBMIT  
INFORMATION DISCLOSURE STATEMENT**

In accordance with their duty of disclosure under 37 C.F.R. §1.56, Applicants would like to direct the Examiner's attention to the following references which are listed below as **Exhibits 1-34** and on Forms PTO/SB/08B (**Exhibit A**). Applicants respectively request that these references be recorded in connection with the above-identified application.

The following references are attached:

1. Beltman, J.McCormick, F., and Cook, S. J. (1996) The selective protein kinase C inhibitor, Ro-31-8220, inhibits mitogen-activated protein kinase phosphatase-1 (MKP-1) expression, induces c-Jun expression, and activates Jun N-terminal kinase. J Biol Chem 271 (43): 27018-24 [**Exhibit 1**]
2. Engman, H.A., et al., CYP3A4, CYP3A5, and MDR1 in human small and large intestinal cell lines suitable

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for drug transport studies. J Pharm Sci, 2001.  
90(11): p. 1736-51 [Exhibit 2]

3. Frame and Cohen 2001. GSK3 takes centre stage more than 20 years after its discovery. Biochem. J. 359: 1-16 [Exhibit 3]
4. Freund et al. 1998. The cdx-1 and cdx-2 homeobox genes in the intestine. Biochem. Cell Biol. 76: 957-969 [Exhibit 4]
5. He, Y. L., S. Murby, et al. (1998). "Species differences in size discrimination in the paracellular pathway reflected by oral bioavailability of poly(ethylene glycol) and D-peptides." J Pharm Sci 87(5): 626-33 [Exhibit 5]
6. Hilgendorf, C., et al., Caco-2 versus Caco-2/HT29-MTX co-cultured cell lines: permeabilities via diffusion, inside- and outside-directed carrier-mediated transport. J Pharm Sci, 2000. 89(1): p. 63-75 [Exhibit 6]
7. Homma, M., K. Oka, T. Yamada, T. Niitsuma, H. Ihto and N. Takahashi (1992). "A strategy for discovering biologically active compounds with high probability in Chinese herb remedies: An application of Saiboku-to in bronchial asthma." Anal. Biochem. 202:179-187 [Exhibit 7]
8. Kawashima, K., K. Saito, A. Yamada, S. Obara, T. Ozaki and Y. Kano (1997). "Pharmacological properties of traditional medicines. XXIII. Searching for active compounds in the blood and bile

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of rats after oral administrations of extracts of Sansohnin." Biol. Pharm. Bull. 20(11): 1171-4  
[Exhibit 8]

9. Kim et al. 2002. PTEN and TNF-alpha regulation of the intestinal-specific cdx-2 homeobox gene through a PI3K, PKB/Akt, and NF-kB-dependent pathway. Gastroenterology 123: 1163-1178 [Exhibit 9]
10. Laprise et al. 2002. Phosphatidylinositol 3-kinase controls human intestinal epithelial cell differentiation by promoting adherens junction assembly and p38 MAPK activation. J. Biol. Chem. 277(10): 8226-8234 [Exhibit 10]
11. Lorentz et al 1999. Downregulation of the colon tumour-suppressor homeobox gene Cdx-2 by oncogenic ras. Oncogene 18: 87-92 [Exhibit 11]
12. Madara, J.L. and Trier, J.S. (1987) Functional morphology of the mucosa of the small intestine. In Physiology of the gastrointestinal tract, 2nd edition, ed. Johnson, L.R., Raven Press, New York [Exhibit 12]
13. Mariadason et al. 2000. Divergent phenotypic patterns and commitment to apoptosis of Caco-2 cells during spontaneous and butyrate-induced differentiation. J Cell Physiol. 183: 347-54 [Exhibit 13]
14. Mariadason et al. 2001. Down-regulation of beta-catenin TCF signaling is linked to colonic

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epithelial cell differentiation. Cancer Res. 61:  
3465-3471 [Exhibit 14]

15. Moore, J.B. et al., Inhibition of PTH desensitization by inhibition of the G protein-coupled receptor kinase-5 enzyme with Ro 32-0432, FASEB J. Part II 12, A741 (1998) [Exhibit 15]
16. Morgan, J.F., H.J. Morton, and R.C. Parker, Nutrition of animal cells in tissue culture. I. Initial studies on a synthetic medium. Proceedings of the Society for Experimental Biology and Medicine, 1950. 73(1): p. 1-8. [Exhibit 16]
17. O'Loughlin, E.V., et al., Interleukin 2 modulates ion secretion and cell proliferation in cultured human small intestinal enterocytes. Gut, 2001. 49(5): p. 636-43 [Exhibit 17]
18. Owens RB, Smith HS, Nelson-Rees WA, Springer EL.(1976) Epithelial cell cultures from normal and cancerous human tissues. J Natl Cancer Inst 56(4):843-9 [Exhibit 18]
19. Pang, G., et al., Immunologic, functional, and morphological characterization of three new human small intestinal epithelial cell lines. Gastroenterology, 1996. 111(1): p. 8-18 [Exhibit 19]
20. Pontier C, Pachot J, Botham R, Lenfant B, Arnaud P. (2001) HT29-MTX and CaCo-2/TC7 monolayers as predictive models for human intestinal absorption: role of the mucus layer. J Pharm Sci 90(10):1608-19 [Exhibit 20]

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21. Quaroni A, Hochman J. (1996) Development of intestinal cell culture models for drug transport and metabolism studies. Adv Drug Del Rev 22:3-52 [Exhibit 21]
22. Rininger J.A.(2001) Utility of a Bioassay-Based Quality Standards Testing Program (BioFit) for Botanical Products in Examining The Science Behind Nutraceuticals. Proceedings of the AAPS Dietary Supplements Forum. P83-95 [Exhibit 22]
23. Sears et al. 2000. Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. Genes Dev. 14: 2501-2514 [Exhibit 23]
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25. Soubeyran et al 2001. Homeobox gene cdx1 regulates ras, rho, and PI3 kinase pathways leading to transformation and tumorigenesis of intestinal epithelial cells. Oncogene 20: 4180-4187 [Exhibit 25]
26. Sun, D., H. Lennernas, et al. (2002). "Comparison of human duodenum and Caco-2 gene expression profiles for 12,000 gene sequences tags and correlation with permeability of 26 drugs." Pharm Res 19(10): 1400-16 [Exhibit 26]

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27. Teoh DA, Kamieniecki D, Pang G, Buret AG. (2000) Giardia lamblia rearranges F-actin and alpha-actinin in human colonic and duodenal monolayers and reduces transepithelial electrical resistance. J Parasitol 86(4):800-6 [Exhibit 27]
28. Wang, et al. 2001. Inhibition of the phosphatidylinositol 3-kinase pathway contributes to HT29 and Caco-2 intestinal cell differentiation. Gastroenterology 120: 1381-1392 [Exhibit 28]
29. Wang, et al. 2002. Regulation of TRAIL expression by the phosphatidylinositol 3-kinase/Akt/GSK-3 pathway in human colon cancer cells. J. Bio. Chem. 277(39): 36602-36610 [Exhibit 29]
30. Watson, et al. 2001. Functional modeling of tight junctions in intestinal cell monolayers using polyethylene glycol oligomers. Am J Physiol Cell Physiol. 281: C388-C397 [Exhibit 30]
31. Van de Wetering et al. 2002. The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. Cell 111: 241-250 [Exhibit 31]
32. Wiren, M., K.E. Magnusson, and J. Larsson, The role of glutamine, serum and energy factors in growth of enterocyte-like cell lines. Int J Biochem Cell Biol, 1998. 30(12): p. 1331-6 [Exhibit 32]
33. Yee, S. (1997). "In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small

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intestinal) absorption in man--fact or myth." Pharm  
Res 14(6): 763-6 [Exhibit 33]

34. Yu, AS (2000) Paracellular solute transport: more  
than just a leak? Curr. Opin. Nephrol. Hypertens.  
9(5): 513-515 [Exhibit 34]

If a telephone interview would be of assistance in advancing  
prosecution of the subject application, Applicants'  
undersigned attorney invites the Examiner to telephone him at  
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No fee is deemed necessary in connection with the filing of  
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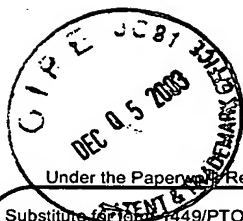
Respectfully submitted,

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### Complete if Known

Application Number 10/648,081

Filing Date August 25, 2003

First Named Inventor LIN, et al.

Art Unit

Examiner Name

Sheet

1

of

4

Attorney Docket Number 784-A-US

### OTHER PRIOR ART—NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	1	Beltman, J. McCormick, F., and Cook, S. J. (1996) The selective protein kinase C inhibitor, Ro-31-8220, inhibits mitogen-activated protein kinase phosphatase-1 (MKP-1) expression, induces c-Jun expression, and activates Jun N-terminal kinase. J Biol Chem 271 (43): 27018-24	
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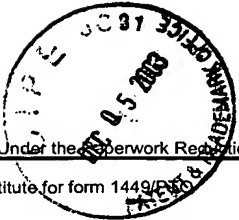
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (Use as many sheets as necessary)		<b>Compl t if Known</b>	
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		Filing Date	August 25, 2003
		First Named Inventor	LIN, et al.
		Art Unit	
Examiner Name			
Sheet 2	of 4	Attorney Docket Number	784-A-US

OTHER PRIOR ART—NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
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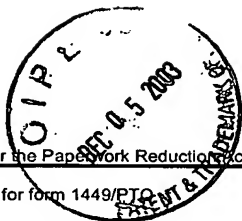
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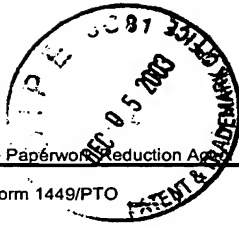
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